

REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated March 12, 2007 are respectfully requested.

I. Amendments

Claims 21 and 27 are amended to recite "the sequence of SEQ ID NO:2, or a sequence consisting of at least 90% homology thereto." Basis for these amendments can be found, for example, on page 172, lines 19-23.

No new matter is added by way of these amendments.

II. Rejections Under 35 U.S.C. § 112, first paragraph

Claims 21-22, 25-27, and 263-266 were rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 21-22, 25-27, and 263-266 were further rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the enablement requirement.

These rejections are respectfully traversed.

1. Written Description

The Examiner asserts that "the specification does not demonstrate possession of the genus of molecules now set forth in the claims" (Office action mailed March 12, 2007, page 3). Although Applicants do not necessarily agree with the rejection, the claims are amended to recite a composition for regenerating nerves, including a Pep5 polypeptide consisting of the sequence of SEQ ID NO:2 or a sequence consisting of at least 90% homology to SEQ ID NO:2 which retains the biological activity of Pep5.

The specification describes the Pep5 polypeptide, for example, on page 61, lines 23-34. The Pep5 protein was sequenced and the sequence is given as SEQ ID NO:2 (page 61, lines 25-27). Procedures for making variants of SEQ ID NO:2 which have 90% homology to SEQ ID NO:2 and retain its activity are conventional in the art. The genus of polypeptides is limited to SEQ ID NO:2 and variants which have

90% homology to SEQ ID NO:2 and which retain the biological activity of Pep5. The specification teaches a variety of assays that one of skill the art can perform to verify that the amino acid change does not result in loss of peptide activity. Applicants teach that the activity of a Pep5 peptide, which binds to p75 and serves to inhibit Rho, can be measured "with a Rho activity assay which blocks activation of Rho by a myelin-derived protein, or the like" (see page 61, lines 30-32). Such assays include immunological assays and phosphorylation quantification (see page 175, lines 5-14). Furthermore, in Examples 2-6 through 2-9, Applicants disclose an *in vivo* nerve regeneration assay that can be performed using variants of Pep5 (see page 353, line 4 through page 354, line 8).

Accordingly, Applicants submit that the specification demonstrates possession the claimed invention.

2. Enablement

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention without undue experimentation (e.g., *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

The Examiner states that the specification is enabling for a composition consisting of the protein of SEQ ID NO:2 with or without a C-terminal alanine. Applicants have amended claims 21 and 27 to be directed towards a composition for regenerating nerves, including a Pep5 polypeptide consisting of the sequence of SEQ ID NO:2 or a sequence consisting of at least 90% homology to SEQ ID NO:2 which retains the biological activity of Pep5. Applicants respectfully submit that amended claims 21 and 27 as well as claims dependent thereon are enabled by the specification. The specific sequence is disclosed in the specification as well as exemplary modifications.

Some experimentation would be expected by one skilled in the art in practicing the claimed method. Those skilled in the art can easily determine whether modifications to the Pep5 polypeptide with at least 90% homology to SEQ ID NO:2

retain the biological activity of Pep5 as described above in section 1. Such experimentation would be routine to one skilled in the art and, therefore, cannot be considered undue.

Accordingly, Applicants submit that the specification would enable any person skilled in the art to which it pertains to make and use the claimed invention.

In light of the above, Applicants submit that the present claims satisfy the requirements of §112, first paragraph and respectfully request that the rejections be withdrawn.

III. Rejections Under 35 U.S.C. § 103

Claims 21-22, 25-27, and 263-266 were rejected under 35 U.S.C. §103(a) as allegedly obvious over Ilag *et al.* in view of Schwarze *et al.* (*Science*, 285:1569-1572, 1999), Voet *et al.* (*Biochemistry*, Second Edition, pp. 58–59, 1995), and Bertin *et al.* (U.S. Patent Publication 2002/0061833).

These rejections are respectfully traversed for the following reasons.

A. The Present Claims

Claim 21 relates to a composition for regenerating nerves, comprising an agent capable of inhibiting a p75 signal transduction pathway, wherein the agent is a Pep5 polypeptide consisting of the sequence of SEQ ID NO:2, or a sequence consisting of at least 90% homology thereto, which retains the biological activity of Pep5; and wherein the agent also comprises a PTD domain.

Claim 27 relates to a similar composition as in claim 21, wherein the composition is suitable for *in vivo* or *in vitro* administration forms.

B. The Applied Art

ILAG ET AL. describe methods for identifying nucleic acid sequences which encode two or more specific interacting peptides or proteins.

SCHWARZE ET AL. describe fusion proteins that contain an NH₂-terminal 11-amino acid protein transduction domain (PTD) for transduction of proteins.

VOET ET AL. list the amino acids and their residue mass.

BERTIN ET AL. relate to a method for determining whether a test compound alters the binding of CARD-3 to p75.

C. Analysis

According to the M.P.E.P. § 2143, "to establish a *prima facie* case of obviousness, three basic criteria must be met. First there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

The present claims are directed to a composition for regenerating nerves comprising an agent capable of inhibiting a p75 signal transduction pathway, wherein the agent is a Pep5 polypeptide or a sequence consisting of at least 90% homology thereto, wherein the agent also comprises a PTD domain. The cited references, alone or in combination, fail to show or suggest the claims as a whole, including the nature of the results obtained.

Ilag *et al.* teach that a peptide of SEQ ID NO:2 can interact with the intracellular domain of p75. The reference does not, however, show or suggest any further role of Pep5 or that this interaction can be exploited for regeneration of nerves. None of the Schwarze *et al.*, Voet *et al.*, or Bertin *et al.* provides the missing teaching. Although Schwarze *et al.* teach fusion proteins containing an 11-amino acid PTD, this reference merely describes the introduction of the proteins into cells and provides no motivation or guidance for modification of a Pep5 polypeptide. Voet *et al.* merely gives some physical data for the amino acids. Bertin *et al.* was cited for teaching "proteins which bind to the intracellular domain of p75 can inhibit cell death" (page 6, Office action mailed March 12, 2007). However, Bertin *et al.* is limited to a teaching that a particular protein, CARD-3, binds to a particular domain (the death domain, which is a specific portion of the "intracellular domain", see paragraph

[0092]) of p75 via a specific motif, the CARD domain (see paragraph [0094]. Furthermore, this interaction is described as being dependent on NGF (see paragraphs [0090] and [0096]). With a careful reading of Bertin *et al.*, one skilled in the art would have no reasonable expectation of successfully achieving results in nerve regeneration with Pep5, or any other protein, due to the very specific interaction described in Bertin *et al.* Nor can Bertin *et al.* reasonably provide motivation to include a PTD domain or the like on Pep5 as the interaction described with respect to CARD-3 and p75 is highly specific. Accordingly, this interaction would not be considered broadly for other proteins, especially given the complexity of the p75 pathway and the multitudinous molecular interactions (both intracellular and extracellular) involved. Finally, Bertin *et al.* is concerned with inhibiting apoptosis and in the identification of compounds which modulate apoptosis. This is NOT equivalent to nerve regeneration as in the presently claimed method.

As a further indicator of non-obviousness, Applicants enclose herewith an announcement by The Ameritec Foundation that the named inventor, Dr. Toshihide Yamashita, was awarded the 2005 Ameritec Prize for his "significant" and "unexpected" accomplishments toward a cure for paralysis, these accomplishments based at least in part on the subject matter of the instant application.

In addition, Applicants enclose two post-filing peer-review journal articles which relate to the claimed subject matter and illustrate its importance in the field, and demonstrate that the technology is and has been adopted for use by others, an indicia of non-obviousness.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

IV. Conclusion

In view of the foregoing, Applicants submit that the claims pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or believes a telephone conference would

expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,
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